Appendix A

1 Betacellulin accelerates the β cell neogenesis, and improves glucose intolerance in diabetic mice

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Betacellulin(BTC), one of the growth factors of EGF family, is expressed in normal pancreas especially during the fetal period, suggesting that this growth factor may play some roles in the ontogeny of the pancreas. To elucidate the role of BTC in the development of pancreatic endocrine cells, we examined the effect of BTC on the morphological and functional changes in pancreatic acinar cell line, AR42J cells. Interestingly, BTC could induce the differentiation from non-endocrine AR42J cells into insulin-secreting cells.

On the other hand, in the pancreas of diabetic mice, the overexpression of BTC and activin A could be observed in tduct cells of the β cell-depleted area. To test the hypothesis that BTC may also act on the regeneration of β cells by the process of neogenesis in the diabetic pancreas, we further examined the effect of BTC administration on the pancreas morphology and glucose intolerance using newly developed diabetic model mice induced by selective perfusion of alloxan (100 mg/kg BW). When rec. human BTC was injected subcutaneously (1 μg/g BW, every day), glucose levels in IPGTT (2g/kg BW) were significantly improved at 8 weeks after the treatment compared to those in sham-operated control group. Immunohistochemical and ultrastructural analyses revealed that islet cell clusters (ICCs) containing insulin-positive cells were significantly increased and were localized in contact with duct cell lining. In addition, somatostatin-positive cells with or without IPF1/PDX-1 immunostaining were frequently observed in newly formed ICCs.

These results from in vitro and in vivo studies demonstrated that BTC is one of the important factors for the differentiation of β cells, and the treatment with BTC in diabetic mice improves glucose intolerance by the acceleration of the β cell neogenesis from duct cells.